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(54) Title: PHARMACEUTICAL AND COSMETIC FORMULATIONS

(57) Abstract: Pharmaceutical and cosmetic formulations comprising hydrophobic highly disperse silicon dioxide with a tamped density of 70-400 g/l.

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Pharmaceutical and cosmetic formulations

The invention relates to pharmaceutical and cosmetic formulations which comprise hydrophobic highly disperse silicon dioxide.

In a medicament a distinction is made between two substance groups with different functions, namely active compounds and auxiliary substances.

The active compounds are characterized by their specific pharmacological action. They are the active constituent of a medicament. As such, they are also identified quantitatively on the packaging and on the pack leaflet.

In addition to the actual active compound, medicaments comprise auxiliary substances or also adjuvants in order to convert the active compound into suitable formulations which are active at the desired site of use. A medicament conventionally comprises several auxiliary substances with different functions, for example fillers, binders, disintegrating agents, lubricants, greasing agents or mould release agents.

A large number of auxiliary substances can be resorted to in the development of stable, easy-to-handle and active medicaments from active compound(s) and auxiliary substances.

Highly disperse silicon dioxide, such as, for example, Aerosil® 200, is an important auxiliary substance which is often employed for pharmaceutical and cosmetic formulations.

Highly disperse silicon dioxide is prepared by flame hydrolysis of chlorosilanes and is therefore also called pyrogenic silicon dioxide. It is listed in numerous

pharmacopoeias as follows: "Hochdisperses Siliciumdioxid" (German Pharmacopoeia); "Silica, Colloidal Anhydrous" (European Pharmacopoeia); "Colloidal Silicon Dioxide" (US Pharmacopoeia / National Formulary), "Colloidal Anhydrous Silica" (British Pharmacopoeia) and "Light Anhydrous Silicic Acid" (Japanese Pharmacopoeia).

Highly disperse silicon dioxide can be used, for example, in solid product forms as a flow regulating agent, adsorbent and desiccant and in liquid and semi-solid product forms as a suspension stabilizer and matrix- and gel-forming agent.
It can furthermore be used to increase the mechanical stability and the rate of disintegration of tablets. It can moreover improve the distribution of the active compound. In a few medicaments highly disperse silicon dioxide also functions as the active compound.

Highly disperse, pyrogenic silicon dioxide has a high affinity for water and is wetted completely by this. It is distinguished by hydrophilic properties.

Hydrophobic highly disperse silicon dioxide, such as, for example, Aerosil® R 972, can have significant advantages over hydrophilic highly disperse silicon dioxide in pharmaceutical and cosmetic compositions. Although it is not described in the Pharmacopoeia, it has therefore been used by some pharmaceutical companies for many years. The Red List - the list of medical preparations for Germany - thus names a number of preparations in which Aerosil® R 972 or methylated silicon dioxide is mentioned as an auxiliary substance.

Hydrophobic highly disperse silicon dioxide as a pharmaceutical raw material is described generally by H. P. Fiedler, Lexikon der Hilfsstoffe [Dictionary of Auxiliary Substances], Editio Cantor Verlag, Aulendorf. Aerosil® R 812 and R 972 are dealt with explicitly here. Information

on the use of Aerosil® R 972 in pharmaceutical and cosmetic compositions is moreover to be found in the publication series Pigmente Nr. 49, Aerosil in Pharmazie und Kosmetik [Pigments no. 49, Aerosil in Pharmacy and Cosmetics], Degussa.

Hydrophobic highly disperse silicon dioxide, such as, for example, Aerosil® R 972, is suitable as a flow regulator for hygroscopic, pulverulent substances. By the formation of a layer of Aerosil® R 972 particles on the powder particles, the water (vapour) uptake thereof is reduced or slowed down (H.P. Fiedler, Lexikon der Hilfsstoffe [Dictionary of Auxiliary Substances], Editio Cantor Verlag Aulendorf, 3rd edition, 1989). Furthermore, no film of water forms on the particles of the hydrophobic silicon dioxide itself, so that the adhesive forces between the "coated" powder particles remain low. In this manner, for example, an addition of 0.5 wt.% Aerosil® R 972 acquires the flow properties of maize starch even at high atmospheric humidities (H. v. Czetsch Lindenwald et al., J. Soc. Cosmetics Chemists 16 (1965) 251). On the other hand, if Aerosil® 200, which is hydrophilic, is used, lumping together of hygroscopic substances - even with relatively high Aerosil contents - often cannot be prevented. Hygroscopic powders contained in capsules also remain flowable by an addition of Aerosil® R 972, which is hydrophobic (H.P. Fiedler, Lexikon der Hilfsstoffe [Dictionary of Auxiliary Substances], Editio Cantor Verlag Aulendorf, 3rd edition, 1989).

Aerosil® R 972 can also be employed in the granulation of hygroscopic products, for example plant extracts. This is even possible from aqueous solutions, so that organic solvents can be omitted. Hydrophilic silicon dioxide is unsuitable here.

Aerosil® R 972 moreover improves the properties of powder raw materials. Thus, for example, the scatter value of

kieselguhr is increased eight-fold (F. Gstirner, *Arch. Pharmz.* 300 (1967) 757). Powders moreover retain their consistency, even at high relative atmospheric humidities.

There are also advantages in tablet-making from hygroscopic powders or granules. Hydrophobic highly disperse silicon dioxide is superior here if a slow tablet disintegration or a delayed release of active compound, for example in the case of sustained release formulations, is to be achieved. Hydrophilic silicon dioxide accelerates tablet disintegration in many cases, since it can be wetted by water and promotes the transportation of water into the inside of the tablet in this manner (wick effect). Together with water-swellable compounds, it is therefore also employed as a disintegrating agent. Since hydrophobic silicon dioxide is not wetted by water, it shows no wick effect.

Some specific examples of sustained-release formulations for solid, oral medicament forms with Aerosil® R 972 are described in the following:

In ibuprofen tablets Aerosil® R 972 reduces the release of active compound to a greater degree than hydrophilic highly disperse silicon dioxides (E.M. Samy et al.; Bull. Pharm. Sci. Assiut University 19 (1996) 19).

If acetaminophen or theophylline is subjected to dry granulation with Aerosil® R 972 and the resulting mixture is introduced into capsules, the active compound release rate thereof is reduced drastically. An addition of 0.6 wt.% Aerosil® R 972 is optimum. With this, 80 - 100% of the active compound is released within eight hours (V.R. Sista et al.; Drug Development and Industrial Pharmacy, 22 (1996) 153).

Aspartate tablets or mineral salt-containing gelatine capsules with a slow release of active compound can be prepared using Aerosil® R 972 (O. Gattnar, Slovakian Patent CS 236300, 1985, L. Gyarmati et al., Hungarian Patent HU 26263, 1983). Capsules with a delayed release of active compound are also described by Takeda Chem. Ind. Ltd., Japanese Patent 0 823 9301, 1996. These contain a "network" of water-soluble carboxymethylcellulose and polyvalent salts, in which is enclosed the active compound dissolved in water. According to the patent specification, Aerosil® R 972 serves as an adsorbent.

Aerosil® R 972 is moreover the most effective flow auxiliary in hard gelatine capsule fillings (H.v. Czetsch-Lindenwald et al., J. Soc. Cosmetics Chemists 16 (1965) 251).

Hydrophilic highly disperse silicon dioxide is unsuitable for stabilizing or thickening w/o emulsions, since it migrates into the aqueous phase because of its hydrophilic character (H.v. Czetsch-Lindenwald, *Pharm. Ind.* 27 (1965) 300). In contrast, stabilization is effected with Aerosil® R 972, because this remains in the oily phase as hydrophobic material and builds up a gel structure here. W/o ointments formulated with Aerosil® R 972 thus still remain spreadable 10 to 20°C above their melting point. The release of aqueous active compounds from such bases is furthermore slowed down.

Aerosil® R 972 thickens balsam gels to a considerably lower degree than hydrophilic highly disperse silicon dioxides. This is advantageous if highly disperse silicon dioxide is employed as an active compound carrier or for conversion of paste-like active compounds into pulverulent ones (E. Toricht et al., Pharmazie 32 (1977) 109).

3% Aerosil® R 972 is sufficient for the preparation of 10% ZnO suspensions in oils, while larger amounts of hydrophilic highly disperse silicon dioxide are required in order to achieve the same effect. After storage for 100 days, according to H.v. Czetsch-Lindenwald, *Pharm. Ind.* 27 (1965) 300, gels form, which can easily be liquefied again by shaking. The content of Aerosil® R 972 is not noticed on the skin.

Highly disperse silicon dioxide is a valuable auxiliary substance in the preparation of suppositories: It prevents the sedimentation of suspended active compounds during pouring and solidification by increasing the viscosity of the molten base, influences - for example in eutectic mixtures - the melting properties and the breaking strength of the products, and can be used as a carrier for incorporation of liquid auxiliary substances. Here also hydrophobic highly disperse silicon dioxide has advantages over the hydrophilic variant in a number of uses (H. Rupprecht et al., Deutsche Apotheker Zeitung 11 (1978) 385).

Thus, the viscosity of molten hard fat which contains 4 wt.% aminophenazone is increased considerably by 4 wt.% Aerosil® R 972, while the effect of 4 wt.% hydrophilic highly disperse silicon dioxide is low (H. Rupprecht et al., Deutsche Apotheker Zeitung 11 (1978) 385). A uniform distribution of the active compound in the suppository mass can be ensured more easily with Aerosil® R 972 in this manner than with hydrophilic highly disperse silicon dioxide. The former moreover slows down the release of the active compound to a greater degree than the latter (H. Rupprecht et al. Pharmazie 32 (1977) 354). The delayed release of a water-soluble active compound from a Witepsol W 35 suppository mass prepared with 2% Aerosil® R 972 is described in H.v. Czetsch-Lindenwald, Pharm. Ind. 27 (1965)

300. Suppositories with sustained release of active compound which comprise the water-soluble active compound morphine sulfate, a swellable organic compound (hydroxypropylmethylcellulose) and Aerosil® R 972 are described by T. Jauw, European Patent 550 100 B1, 1996.

Medical patches, the adhesive layer of which comprises in each case 7.1 wt.% of Aerosil® R 972 and hydrophilic highly disperse silicon dioxide (based on the dry matter), in addition to the active compound and various polymers, are described by Sekisui Chem. Ind. Com. Ltd., *Japanese Patent* 0 625 6178, 1996 and Sekisui Chem. Ind. Com. Ltd., *Japanese Patent* 0 625 6173, 1994 and *Japan. Patent* 0 431 2525, 1992). Aerosil® R 972 and hydrophilic highly disperse silicon dioxide increase the viscosity of the solution containing polymer and active compound which is applied to the support and dried. The active compounds are optionally also adsorbed on to the surface of the highly disperse silicon dioxide, the consequence of which is a slower and more uniform release of the active compound.

Aerosil® R 972 and R 812 are furthermore employed for the preparation of pharmaceutical and cosmetic formulations bottled in pressurized gas bottles (H. v. Czetsch Lindenwald et al., *J. Soc. Cosmetics Chemists* 16 (1965) 251).

Injection solutions based on Aerosil® R 974-containing w/o emulsions are described, for example, in EP 1 179 349 A1.

Since the highest purity requirements must be met in the preparation of pharmaceutical and cosmetic products, the considerable development of dust in particular presents

problems when working with hydrophobic highly disperse silicon dioxide types - commercially available products are, for example, Aerosil® R 972 and Aerosil® R 974 (both Degussa), Wacker HDK H15 and Wacker HDK H20 (both Wacker) and Cab-O-Sil TS 610 and Cab-O-Sil TS 620 (both Cabot). Since hydrophobic highly disperse silicon dioxide types as a rule have finer particles than the hydrophilic products (e.g. Aerosil® 200), the dust problem is even more serious here. Another disadvantage is the low bulk and tamped density of the hydrophobic product types, typical values are 40-50 g/l, which causes a considerable additional expenditure on labour and time in the preparation of pharmaceutical and cosmetic formulations.

In the use of hydrophobic highly disperse silicon dioxide in pharmaceutical and cosmetic formulations, an improved flowability of mixtures produced with this would furthermore be desirable, in order to be able to achieve, for example, a higher dosing accuracy in the production of tablets and capsules. By this means, it would be possible on the one hand to achieve a lower variation in tablet and capsule weights and on the other hand to improve the profitability of processes which lead to these presentation forms.

The object of the present invention is to provide pharmaceutical and cosmetic formulations which avoid the disadvantages of the prior art.

The invention provides pharmaceutical and cosmetic formulations which comprise hydrophobic highly disperse silicon dioxide, which are characterized in that the silicon dioxide has a tamped density of 70 to 400 g/l, determined in accordance with DIN 55943.

The invention also provides pharmaceutical and cosmetic formulations which comprise hydrophobic highly disperse silicon dioxide, which are characterized in that the silicon dioxide contains a maximum of 3.0 wt.% of water-wettable contents.

The invention also provides pharmaceutical and cosmetic formulations which comprise hydrophobic highly disperse silicon dioxide, which are characterized in that the silicon dioxide has a tamped density of 70 to 400 g/l, determined in accordance with DIN 55943, and contains a maximum of 3.0 wt.% of water-wettable contents.

It has been found that when working with the formulations according to the invention only a low development of dust occurs and the flowability of the formulations is significantly higher than in the case of those according to the prior art. In addition, the mechanical stability of tablets is improved and the capsule weight is increased. Furthermore, the release properties of tablets and capsules can be adjusted in a controlled manner.

This result is surprising, since it was not possible to assume that the properties, such as, for example, flowability or mechanical stability, of the pharmaceutical and cosmetic formulations are influenced by the tamped density of the pyrogenic silicon dioxide used. According to the article "Kolloidale Kieselsäure als Gelbildner [Colloidal silica as a gel-forming agent]" (www.pharmazeutische-zeitung.de/pza/2001-51/pharm.5.htm) it was even to be expected that compacted highly disperse silicas have disadvantages compared with the non-compacted product types. Problems are described here with Aerosil® 200 V (tamped density 120 g/l), since it does not achieve the required thickening performance compared with the standard products Aerosil® 200 (tamped density 50 g/l).

It is furthermore surprising that the release of active compounds and the disintegration time of the pharmaceutical and cosmetic formulations is influenced by the tamped density of the hydrophobic silicon dioxide used.

It has been found that it is particularly favourable to choose a tamped density of the hydrophobic highly disperse silicon dioxide of between 70 and 400 g/l, in particular between 75 and 300 g/l.

It is furthermore advantageous to choose hydrophobic highly disperse silicon dioxide with a BET surface area, determined in accordance with DIN 66131, of 50 to 400 m^2/g. A BET surface area of 90-300 m^2/g is particularly advantageous.

The preparation of the silicon dioxide is known, for example, from Ullmann's Encyclopedia of Industrial Chemistry, vol. A23, page 635 et seq., 5th edition, 1993.

Hydrophilic highly disperse silicon dioxide can be prepared by flame hydrolysis of chlorosilanes and is very pure chemically. It carries silanol groups on its surface. As a result it has a high affinity for water - it is hydrophilic - and is wetted completely by this. Alkyl groups can be anchored chemically on the surface of the substance by reaction of the silanol groups with organic silicon compounds. The resulting products are then no longer wetted by water, they are hydrophobic.

Aerosil® R 972 and Aerosil® R 974 are thus formed by reacting freshly prepared Aerosil® with dimethyldichlorosilane in an inert gas atmosphere at 400 to 600ºC in the presence of water vapour (publication series Pigmente Nr. 5, "Hydrophobes Aerosil, Herstellung, Eigenschaften und Anwendungen" [Pigments no. 5, "Hydrophobic Aerosil, Preparation, Properties and Uses"], Degussa). Aerosil can also be partly or completely

hydrophobized with other organosilanes. Examples of these are Aerosil® R 812 (reaction with hexmethyldisilazane), Aerosil® R 805 (reaction with trimethoxyoctylsilane) and Aerosil® R 202 (with silicone oil). Processes for treatment with a surface-modifying agent are to be found, for example, in DE-A-11 63 784, DE-A-196 16 781, DE-A-197 57 210 or DE-A-44 02 370.

The hydrophobic highly disperse silicon dioxide acquires its tamped density either directly during the preparation or in a subsequent process step. Thus, for example, compacting processes for pyrogenic silicon dioxide are described in DE-A-32 38 427 and DE-A-37 41 846. The high tamped density can furthermore be achieved by a grinding such as is described, for example, in EP 0 637 616 A1. Granules of hydrophobic highly disperse silicon dioxide from EP 0 725 037 also have a high tamped density and are suitable according to the invention for pharmaceutical and cosmetic formulations.

Hydrophobic highly disperse silicon dioxide types which are suitable according to the invention and are already commercially available are Aerosil® R 972 V, Aerosil® R 974 V, Aerosil® R 976 V (Degussa), Aerosil® R 8200 (Degussa), Aerosil® R 972 W (Nippon Aerosil Corporation), Wacker HDK H15P, HDK H2000 and HDK H3004 (Wacker) and Reolosil DM10 (Tokuyama). Aerosil® R 972 V, Aerosil® R 974 V and Aerosil® R 972 W, and compacted Aerosil® R 812 and Aerosil® 812 S are particularly suitable.

Hydrophobic highly disperse silicon dioxide is not wetted by water. Various methods are known for determination of the hydrophobicity or the degree of hydrophobization, for example the methanol wettability of Corning Glass.

A simple method for determination of the water-wettable contents is described in the following: About 0.2 g of substance, weighed accurately to 0.001 g, are shaken

intensively with 50 ml of water in a 250 ml pear-shaped separating funnel for 1 min. The funnel is then left to stand for one hour. During this, the predominant portion of the solid floats up. Without shaking up the suspension again, 45 ml of the liquid, which may be slightly cloudy, are drained off dropwise and transferred to a dish which has been dried at 140°C and cooled in a desiccator. The liquid is evaporated off completely at 110 - 150°C, during which it should be ensured that no substance sprays out. After cooling in a desiccator, the dish is weighed again. The weight difference with respect to the empty dish should be not more than 0.006 g. This corresponds to 3.0 wt.% of the substance weighed out. Hydrophobic highly disperse silicon dioxide in which the water-wettable contents make up a max. of 3.0 wt.% are particularly suitable for the pharmaceutical and cosmetic formulations according to the invention.

Pyrogenic silicon dioxide also includes doped oxides and mixed oxides in which the silicon dioxide content is at least 90%. Doped pyrogenic silicon dioxides can be obtained, for example, by the process described in DE-A-196 50 500, in which the doping is introduced via an aerosol of a salt solution or suspension in a flame such as is used for the preparation of pyrogenic oxides. A mixed oxide with a silicon dioxide content of greater than 90 wt.% can be obtained, for example, by the process described in DE-A-199 19 635.

Mixtures of pyrogenic silicon dioxide with doped silicon dioxide with an SiO_2 content of 90%, with mixed oxides with an SiO_2 content of 90% or more and/or hydrophobized silicon dioxide can also be used for the formulations according to the invention.

The hydrophobic highly disperse silicon dioxide is preferably present in the formulation according to the

invention to the extent of 0.01 to 30 wt.%, particularly preferably to the extent of 0.1 to 15.0 wt.%. It is conventionally employed as an auxiliary substance, but can also be used as an active compound, the action then primarily being a physical action.

Hydrophobic highly disperse silicon dioxide with a tamped density of between 70 and 400 g/l can be employed according to the invention in any desired solid, semi-solid or liquid pharmaceutical formulations (medicament forms), preferably for oral and/or topical uses, for example in suspensions, emulsions, aerosols, injection solutions, ointments, creams, gels, pastes, suppositories, sticks, powders, dusting powders, granules, tablets, pastilles, coated tables, film-coated tablets, hard gelatine capsules, soft gelatine capsules, extrudates, microcapsules or microspherules. Solid medicament forms, such as, for example, powders, dusting powders, granules, tablets and capsules, are particularly preferred.

The term pharmaceutical formulations in the context of the present invention also includes precursors and intermediates products for the preparation of granules, tablets, capsules, suspensions, inspissated juices and inspissated drops. Such precursors and intermediate products can have e.g. the form of a powder, granules or an extrudate.

Methods for the preparation of solid, semi-solid and liquid medicament forms are known and are described in numerous publications and textbooks of pharmaceutical technology, cf. for example K.H. Bauer, K.-H. Frömming, C. Führer, Lehrbuch der pharmazeutischen Technologie [Textbook of Pharmaceutical Technology], 6th edition, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart 1999.

The formulations according to the invention can comprise any desired pharmaceutical active compound. Examples which

may be mentioned are: α-proteinase inhibitor, abacavir, abciximab, acarbose, acetylsalicylic acid, acyclovir, adenosine, albuterol, aldesleukin, alendronate, alfuzosin, alosetron, alprazolam, alteplase, ambroxol, amifostine, amiodarone, amisulpride, amlodipine, amoxicillin, amphetamine, amphotericin, ampicillin, amprenavir, anagrelide, anastrozole, ancrod, anti-haemophilia factor, aprotinin, atenolol, atorvastatin, atropine, azelastine, azithromycin, azulene, barnidipine, beclomethasone, benazepril, benserazide, beraprost, betamethason, betaxolol, bezafibrate, bicalutamide, bisabolol, bisoprolol, botulinus toxin, brimonidine, bromazepam, bromocriptine, budesonide, bupivacaine, bupropion, buspirone, butorphanol, cabergoline, calcipotriene, calcitonin, calcitriol, camphor, candesartan, candesartan cilexetil, captopril, carbamazepine, carbidopa, carboplatin, carvedilol, cefaclor, cefadroxil, cefaxitin, cefazolin, cefdinir, cefepime, cefixime, cefmetazole, cefoperazone, cefotiam, cefoxopran, cefpodoxime, cefprozil, ceftazidime, ceftibuten, ceftriaxone, cefuroxime, celecoxib, celiprolol, cephalexin, cerivastatin, cetirizine, chloramophenicol, cilastatin, cilazapril, cimetidine, ciprofibrate, ciprofloxacin, cisapride, cisplatin, citalopram, clarithromycin, clavulanic acid, clindamycin, clomipramine, clonazepam, clonidine, clopidogrel, clotrimazole, clozapine, cromolyn, cyclophosphamide, cyclosporin, cyproterone, dalteparin, deferoxamine, desogestrel, dextroamphetamine, diazepam, diclofenac, didanosine, digitoxin, digoxin, dihydroergotamine, diltiazem, diphtheria protein, diphtheria toxoxide, divalproex, dobutamine, docetaxel, dolasetron, donepezil, dornase-α, dorzolamide, doxazosin, doxifluridine, doxorubicin, dydrogesterone, ecabet, efavirenz, enalapril, enoxaparin, eperison, epinastine, epirubicin, eptifibatide, erythropoietin-α, erythropoietin-β, etanercept, ethinyloestradiol, etodolac, etoposide, factor VIII, famciclovir, famotidine, faropenem,

felodipine, fenofibrate, fenoldopam, fentanyl, fexofenadine, filgrastim, finasteride, flomoxef, fluconazole, fludarabine, flunisolide, flunitrazepam, fluoxetine, flutamide, fluticasone, fluvastatin, fluvoxamine, follitropin-α, follitropin-β, formoterol, fosinopril, furosemide, gabapentin, gadodiamide, ganciclovir, gatifloxacin, gemcitabin, gestodene, glatiramer, glibenclamide, glimepiride, glipizide, glyburide, goserelin, granisetron, griseofulvin, hepatitis B antigen, hyaluronic acid, hycosin, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphone, hydroxychloroquine, hylan g-f 20, ibuprofen, ifosfamide, imidapril, imiglucerase, imipenem, immunoglobulin, indinavir, indomethacin, infliximab, insulin, insulin, human, insulin lispro, insulin aspart, interferon-β, interferon-α, iodine-125, iodixanol, iohexol, iomeprol, iopromide, iopromide, ioversol, ioxoprolen, ipratropium, ipriflavone, irbesartan, irinotecan, isosorbide, isotretinoin, isradipine, itraconazole, potassium chlorazepate, potassium chloride, ketorolac, ketotifen, whooping-cough vaccine, coagulation factor IX, lamivudine, lamotrigin, lansoprazole, latanoprost, leflunomide, lenograstim, letrozole, leuprolide, levodopa, levofloxacin, levonorgestrel, levothyroxine, lidocaine, linezolid, lisinopril, lopamidol, loracarbef, loratadine, lorazepam, losartan, lovastatin, lysine-acetylsalicylic acid, manidipin, mecobalamin, medroxyprogesterone, megestrol, meloxicam, menatetrenone, meningococcus vaccine, menotropin, meropenem, mesalamine, metaxalone, metformin, methylphenidate, methylprednisolone, metoprolol, midazolam, milrinone, minocycline, mirtazapine, misoprostol, mitoxantrone, moclobemide, modafinil, mometasone, montelukast, morniflumate, morphium, moxifloxacin, mycophenolate, nabumetone, nadroparin, naproxen, naratriptan, nefazodone, nelfinavir, nevirapine, niacin, nicardipine, nicergoline, nifedipine, nilutamide, nilvadipine, nimodipine, nitroglycerine, nizatidine,

norethyndron, norfloxacin, octreotid, olanzapin, omeprazole, ondansetron, orlistat, oseltamivir, oestradiol, oestrogens, oxaliplatin, oxaprozin, oxolinic acid, oxybutynin, paclitaxel, palivizumab, pamidronate, pancrelipase, panipenem, pantoprazole, pantoprazole, paracetamol, paroxetine, pentoxifylline, pergolide, phenytoin, pioglitazon, piperacillin, piroxicam, pramipexole, pravastatin, prazosin, probucol, progesterone, propafenone, propofol, propoxyphen, prostaglandin, quetiapine, quinapril, rabeprazole, raloxifene, ramipril, ranitidine, repaglinide, reserpine, ribavirin, riluzole, risperidone, ritonavir, rituximab, rivastigmine, rizatriptan, rofecoxib, ropinirole, rosiglitazon, salmeterol, saquinavir, sargramostim, serrapeptase, sertraline, sevelamer, sibutramine, sildenafil, simvastatin, somatropin, somatropin, sotalol, spironolactone, stavudine, sulbactam, sulfaethidole, sulfamethoxazole, sulfasalazine, sulpiride, sumatriptan, tacrolimus, tamoxifen, tamsulosin, tazobactam, teicoplanin, temocapril, temozolomide, tenecteplase, tenoxicam, teprenone, terazosin, terbinafine, terbutaline, tetanus toxoid, tetrabenazine, tetrazapam, thymol, tiagabine, tibolone, ticarcillin, ticlopidine, timolol, tirofiban, tizanidine, tobramycin, tocopheryl nicotinate, tolterodine, topiramate, topotecan, torasemide, tramadol, trandolapril, trastuzumab, triamcinolone, triazolam, trimebutine, trimethoprim, troglitazone, tropisetron, tulobuterol, unoprostone, urofollitropin, valacyclovir, valproic acid, valsartan, vancomycin, venlafaxine, verapamil, verteporfin, vigabatrin, vinorelbine, vinpocetine, voglibose, warfarin, zafirlukast, zaleplon, zanamivir, zidovudine, zolmitriptan, zolpidem, zopiclone and derivatives thereof. However, pharmaceutical active compounds are also to be understood as meaning other substances, such as vitamins, provitamins, essential fatty acids, extracts of plant and animal origin and oils of plant and animal origin.

The pharmaceutical compositions in which hydrophobic highly disperse silicon dioxide with a tamped density of between 70 and 400 g/l can be employed also include plant medicament formulations and homoeopathic formulations.

The pharmaceutical formulations according to the invention can also be so-called sustained release and depot medicament forms with controlled release of the active compounds. The pharmaceutical formulations according to the invention can furthermore also be part of therapeutic systems, such as, for example, therapeutic systems for local use and transdermal therapeutic systems.

Further constituents of the pharmaceutical compositions can be conventional auxiliary substances, such as, for example, antioxidants, binders, emulsifiers, dyestuffs, film-forming agents, fillers, aroma substances, flavourings, gel-forming agents, preservatives, solvents, oils, powder bases, ointment bases, acids and salts for recipe formulation, small-scale preparation and preparation of pharmaceutical compositions, greasing agents, disintegrating agents, suppository bases, suspension stabilizers, sweeteners, propellant gases, plasticizers and sugar substitutes.

According to an advantageous embodiment, the formulations according to the invention can comprise as the active compound paracetamol, acetylsalicylic acid or ibuprofen.

The hydrophobic highly disperse silicon dioxide with a tamped density of between 70 and 400 g/l can furthermore be used according to the invention in cosmetic formulations of any desired consistency, for example in powders, liquids, foams, sprays, gels, creams, ointments, pastes, sticks or tablets. The cosmetic formulations can accordingly be single- or multi-phase systems, such as, for example, emulsions, suspensions or aerosols.

The cosmetic formulation according to the invention can be, for example, a soap; a syndet; a liquid washing or shower preparation; a bath additive; a make-up removal composition; a peeling preparation; a skin cream; a skin lotion; a face mask; a foot care composition; a sunscreen composition; a skin tanning composition; a depigmenting composition; an insect-repellent composition; a wet shaving composition, such as, for example, a stick, a cream, a gel or a foam; a pre-shave preparation; an after-shave care composition; a hair removal composition; a dental cream; a hair shampoo; a hair care composition, such as, for example, a hair treatment course, a rinse or a conditioner; a permanent wave composition; a straightening composition, a style setting composition, such as, for example, a hair setting composition, a hair spray, a hair lacquer, a hair gel or a hair wax; a hair colour-modifying composition, such as, for example, a blonding composition, a hair-colouring composition, a toner or a colour enhancer; a deodorant or an antiperspirant composition, such as, for example, a stick, a roll-on, a lotion, a powder or a spray; a face make-up, such as, for example, a tinted day cream, a powder cream, a face powder, a cream make-up or a rouge; an eye make-up, such as, for example, a lid shadow, a mascara, a kajal stick, an eyeliner or an eyebrow pencil; a lip care composition; a decorative lip care composition, such as, for example, a lipstick, a lip gloss or a lip contour pencil; or a nail care composition, such as, for example, a nail varnish, a nail varnish remover, a cuticle remover, a nail hardener or a nail care cream.

The present invention also provides a cosmetic formulation which comprises the hydrophobic highly disperse silicon dioxide and at least one constituent chosen from absorbents, astringents, antimicrobial substances, antioxidants, antiperspirants, antifoams, antidandruff active compounds, antistatics, binders biological additives, bleaching agents, chelating agents, deodorizing

agents, emollients, emulsifiers, emulsion stabilizers, depilatory agents, dyestuffs, humectants, film-forming agents, aroma substances, flavourings, hair-colouring agents, preservatives, corrosion protection agents, cosmetic oils, solvents, oral care substances, oxidizing agents, plant constituents, buffer substances, reducing agents, abrasives, surfactants, propellant gases, opacifying agents, UV filters and absorbers, denaturants, viscosity regulators and vitamins.

Examples

Pharmaceutical formulations:

The pulverulent starting substances are weighed accurately to 0.01 g in the stated sequence and mixed manually in a glass bottle. This mixture is sieved through a sieve of mesh width 0.71 mm and homogenized in a glass bottle with a Turbula mixer for five minutes.

Table 1: Formulations (data in wt.%)

	Formulation 1	Formulation 2	Formulation 3
Paracetamol	83.3	-	-
Acetylsalicylic acid	-	83.3	-
Lactose	-		79.7
Powdered cellulose	13.3	10.4	20.0
Maize starch	3.0	5.0	-
Magnesium stearate	0.1	-	-
Stearic acid	-	1.0	-
Silicon dioxide	0.3	0.3	0.3

Aerosil® R 972 (tamped density approx. 50 g/l; comparison examples) and Aerosil® R 972 V (tamped density 90 g/l; according to the invention) are used as the silicon dioxide.

The flow rating and/or poured cone height are determined as a measure of the flowability. Furthermore, tablets are pressed and capsules filled with the formulations according to table 1.

Hard gelatine capsules

Using a capsule filling apparatus, hard gelatine capsules of size 1 with an empty weight of 71 - 78 mg are filled with the formulations according to table 1. In each case 60 capsules are prepared and the average capsule weight is determined.

The values for formulation 1 are to be found in tab. 2, those for formulation 2 in tab. 3 and those for formulation 3 in tab. 4.

Tablets

The formulations according to table 1 are pressed at the same pressing pressure using an eccentric press (EKO, Korsch) to give tablets with a weight of approx. 600 mg. The tablet hardness is determined on in each case 10 tablets by means of a semi-automatic hardness tester. The disintegration time in water warmed to 37°C (manufacturer Erweka, model ZT 31) is moreover determined on six tablets.

The values for formulation 1 are to be found in tab. 2, those for formulation 2 in tab. 3 and those for formulation 3 in table 4.

Table 2: Properties of formulation 1

Tamped density SiO_2 [g/l]	Poured cone height (cm)	Tablet hardness [N]	Disintegration time [s]	Capsule weight [mg]
50	2.4	59	25	380
90	2.2	79	30	399

*Poured cone height determined in accordance with:Publication series Pigmente [Pigments], number 31 from Degussa, 6th edition. The lower the poured cone height of a powder mixture, the better the flow properties.

Table 3: Properties of formulation 2

Tamped density SiO_2 [g/l]	Poured cone height [cm]	Tablet hardness [N]	Disintegration time [s]	Capsule weight [mg]
50	2.4	93	25	375
90	2.2	95	35	381

Table 4: Properties of formulation 3

Tamped density SiO_2 [g/l]	Poured cone height [cm]	Tablet hardness [N]	Disintegration time [s]	Capsule weight [mg]
50	2.3	141	25	345
90	2.2	238	75	350

The formulations according to the invention show clear advantages in flow properties, tablet hardness and capsule weight. They moreover have a longer disintegration time.

Pharmaceutical auxiliary substance mixtures:

198.0 g Avicel PH101 and in each case 2.0 g Aerosil® R 972 (Degussa; tamped density 50 g/l; comparison example), Aerosil® R 972 V (Degussa; tamped density 90 g/l; according to the invention) and Aerosil® R 972 W (Nippon Aerosil Corporation; tamped density 160 g/l) are premixed manually in a 1 l wide-necked bottle and the mixture is sieved through a 0.71 mm sieve and mixed in a free-fall mixer (Turbula) for 10 min at 42 revolutions per minute. The flow rating and poured cone height of the mixture were then determined.

The results of the experiments are summarized in table 5.

Table 5: Properties of the pharmaceutical auxiliary substance mixtures

Tamped density SiO_2 [g/l]	Flow rating	Poured cone height [cm]
50	3	2.0
90	2.5	1.9
160	2	1.75

*Flow rating and poured cone height determined in accordance with: Publication series Pigmente [Pigments], number 31 from Degussa, 6th edition. The lower the flow rating or poured cone height of a powder mixture, the better the flow properties.

Determination of the water-wettable contents of hydrophobic highly disperse silicon dioxide:

About 0.2 g of substance, weighed accurately to 0.001 g, are shaken intensively with 50 ml of water R in a 250 ml pear-shaped separating funnel for 1 min. The funnel is then left to stand for one hour. During this, the predominant portion of the solid floats up. Without shaking up the suspension again, 45 ml of the liquid, which may be slightly cloudy, are drained off dropwise and transferred to a dish which has been dried at 140°C and cooled in a desiccator.

The liquid is evaporated off completely at 110 - 150°C, during which it should be ensured that no substance sprays out. After cooling in a desiccator, the dish is weighed again. The weight difference with respect to the empty dish should be not more than 0.006 g. This corresponds to 3.0 wt.% of the substance weighed out.

Table 6: Water-wettable contents of the hydrophobic highly disperse silicas used

Product	Aerosil® 972	Aerosil® 972 V	CP 1	CP 2
Tamped density (g/l)	50	90	50	90
Water-wettable contents (%)	3.0	2.0	7.0	6.0

The comparison products CP 1 and CP 2 are prepared analogously to Aerosil® R 972 and Aerosil® R 972 V, but with a starting amount of dimethyldichlorosilane reduced by 10%. The products therefore have a somewhat higher content of water-wettable contents. Pharmaceutical formulations 2 and 3 from table 1 are also prepared with CP 1 and CP 2. The analytical data of the formulations are summarized in tables 7 and 8.

Table 7: Properties of formulation 2

Product	Poured cone height [cm]	Tablet hardness [N]	Disintegration time [s]	Capsule weight [mg]
Aerosil ® R 972	2.4	93	25	375
CP 1	2.6	80	15	355
Aerosil ® R 972 V	2.2	95	35	381
CP 2	2.4	88	20	368

Table 8: Properties of formulation 3

Product	Poured cone height [cm]	Tablet hardness [N]	Disintegration time [s]	Capsule weight [mg]
Aerosil ® R 972	2.3	141	25	345
CP 1	2.5	125	20	335
Aerosil ® R 972 V	2.2	238	75	350
CP 2	2.4	202	60	340

The experiments show that in addition to the tamped density, the water-wettable contents have a considerable influence on the properties of the pharmaceutical formulations. Hydrophobic highly disperse silicon dioxide in which the water-wettable contents make up a max. of 3.0 wt.% are accordingly particularly suitable for the

pharmaceutical and cosmetic formulations according to the invention.

Patent claims:

1. Pharmaceutical and cosmetic formulations comprising hydrophobic highly disperse silicon dioxide, characterized in that the silicon dioxide has a tamped density of 70 to 400 g/l.

2. Formulations according to claim 1, characterized in that the BET surface area of the hydrophobic highly disperse silicon dioxide is between 50 and 400 m^2/g.

3. Formulations according to claim 1 or 2, characterized in that the hydrophobic highly disperse silicon dioxide is present in the formulations to the extent of 0.01 to 30 wt.%.

4. Formulations according to claim 1 or 2 comprising hydrophobic highly disperse silicon dioxide, characterized in that the silicon dioxide contains a maximum of 3.0 wt.% of water-wettable contents.

5. Formulations according to claim 1 or 2 comprising hydrophobic highly disperse silicon dioxide, characterized in that the silicon dioxide has a tamped density of 70 to 400 g/l, determined in accordance with DIN 55943, and contains a maximum of 3.0 wt.% of water-wettable contents.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K8/25

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 637 616 A (DEGUSSA) 8 February 1995 (1995-02-08) cited in the application page 2, line 27-32; claims 1,2 page 6 -page 7	1,2
A	US 5 776 240 A (MEYER JUERGEN ET AL) 7 July 1998 (1998-07-07) claim 1	1,2
A	US 4 034 077 A (HILL JOHN ANTHONY ET AL) 5 July 1977 (1977-07-05) claim 1; examples 3-8	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
7 April 2004	19/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kardas-Llorens, E

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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PCT REQUEST

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Original (for **SUBMISSION**) - printed on 22.09.2003 01:00:14 PM

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name:	in relation to this international application DEGUSSA AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1 (ii)		DEGUSSA AG is entitled as employer of the inventor, HASENZAHL, Steffen
VIII-2-1 (ii)		DEGUSSA AG is entitled as employer of the inventor, DRECHSLER, Margarete
VIII-2-1 (ix)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

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VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name:	in relation to the international application No. PCT/EP03/11054 DEGUSSA AG is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1 (ii)		DEGUSSA AG is entitled as employer of the inventor, HASENZAHL, Steffen
VIII-2-1 (ii)		DEGUSSA AG is entitled as employer of the inventor, DRECHSLER, Margarete
VIII-2-1 (ix)	This declaration is made for the purposes of:	all designations except the designation of the United States of America

020475 FH

Original (for **SUBMISSION**) - printed on 14.09.2003 01:00:14 PM

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to international application No. PCT/EP03/11054(if furnishing declaration pursuant to Rule 26ter) I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name:	HASENZAHL, Steffen
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Hanau, Germany
VIII-4-1-1-3	Mailing address:	Hochstädter Landstrasse 113
VIII-4-1-1-4	Citizenship:	DE
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	Steffen Hasenzahl
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	10/23/2003

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VIII-4-1-2-1	Name:	DRECHSLER, Margarete
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Gelnhausen, Germany
VIII-4-1-2-3	Mailing address:	Hintergasse 2
VIII-4-1-2-4	Citizenship:	DE
VIII-4-1-2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	Margarete Drechsler
VIII-4-1-2-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	10/27/2003

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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)*
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(54) Title: PHARMACEUTICAL AND COSMETIC FORMULATIONS

(57) Abstract: Pharmaceutical and cosmetic formulations comprising hydrophobic highly disperse silicon dioxide with a tamped density of 70-400 g/l.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
020475 FH		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP03/11054	07/10/2003	31/10/2002
International Patent Classification (IPC) or national classification and IPC		
A61K9/00		
Applicant		
DEGUSSA AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03/05/2004	16/07/2004
Name and mailing address of the IPEA/	Authorized officer
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I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

In light of the documents cited in the international search report, it is considered that the invention as defined in the claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable.